REMARKS

Claims 16, 17, and 21 to 30 were examined in this application. Claims 1-15 and 18-20 are withdrawn. It is respectfully requested that when the subject matter of claims 16, 17 and 21 to 30 are allowed that claims 1-15, 18, 19 and 20 be rejoined in this application.

In view of the amendment of claim 21, the rejection of claims 21-30 under 35 USC 112 is moot.

According to the Official Action claims 16, 17 and 21 to 30 are rejected under 35 USC §102 (B) and 35 USC §103 (a) as being anticipated or obvious over

(i) Agharkar et al. (US Patent No. 5,504,102);

(ii) Anevski et al. (US Patent No. 6,388,112); and

(iii) Zhang et al. (WO 01/52838)

US Patent No. 5,504,102, (herein after referred to as Agharkar et al.) has a first filing date of September 29, 1993 and essentially relates to a stabilized pharmaceutical composition comprising an antineoplastic compound selected from teniposide, paclitaxel, camptothecin and derivatives thereof, more specifically to a stabilized composition of paclitaxel.

Agharkar et al., while discussing the prior art state that even though, commercial grade Cremophor EL mixed with ethanol as a co-solvent is effective in solubilizing pharmaceutical agents, especially paclitaxel, however such compositions are not stable over extended periods of time.

> "In particular, pharmaceutical compositions of Taxol in a co-solvent of 50:50 by volume of dehydrated ethyl alcohol and commercial grade Cremophor EL exhibit a loss of potency of greater than 60% after storage for 12 weeks at 50°C. The loss of potency is attributed to the decomposition of paclitaxel during storage" [See lines 11-16, Column 2 of Agharkar et al.]

Agharkar et al. describe contacting the commercially available Cremophor EL with a bed of aluminum oxide or by adding an acid, in particular a mineral acid to Cremophor which results in lowering the carboxylate ion content of Cremophor, which in turn when utilized for the preparation of a paclitaxel composition renders the composition stable.

It should be noted that the method utilized by Agharkar et al. for purification of Cremophor involves an adsorption technique wherein the free carboxylate anions as well as impurities present in the commercial Cremophor are "adsorbed" on the alumina bed and are thus separated from Cremophor, which can be isolated in pure form through elution from the column bed. Please refer Lines 49-55, Column 3 of Agharkar et al., which states that purification indeed is achieved through an adsorption technique.

US Patent No. 6,388,112, (hereinafter referred to as Anevski et al.), also cited by the Examiner has a first filing date of Oct 20, 1998, which is much later than that of Agharkar et als September 29, 1993 first filing date.

Interestingly, Anevski et al. also discuss the problems associated with developing a stable paclitaxel composition and offer a solution, which again comprises utilization of a purified Cremophor in the composition, which renders stability to the composition. This is similar to the teaching of Agharkar et al., which was full prior art at the time of filing of the application from which US Patent 6,388,112 was granted.

However, the inventiveness, if any, in the Anevski et al. application is that it is distinguished from Agharkar et al. in the method utilized for purification of Cremophor.

The method taught by Anevski et al. involves a two stage purification of Cremophor, comprising:

(a) forming a solution of commercially available Cremophor and an alcohol and contacting the said solution with an activated carbon column ; and

(b) contacting the solution obtained after carbon treatment from step (a) with an ion exchange resin column, followed by evaporation of residual water and alcohol to give pure Cremophor.

Here again, it should be noted that the first step of purification utilized by Anevski et al. involves an adsorption technique wherein water, unsaturated aliphatic and aromatic compounds present in Cremophor are selectively "adsorbed " on the carbon bed, leaving the filtrate free from such impurities. In the second stage of purification, the partially purified Cremophor, obtained through carbon treatment is passed through an ion-exchange resin column, which selectively exchanges the cations and anions present in Cremophor, thereby leaving behind pure Cremophor, free from impurities and carboxylate anions or other cations. [Please refer Lines 66-67, Column 1 and Lines 1-24, Column 2].

Herein again, the method of purification utilized by Anevski et al. involves an adsorption technique, albeit, through a different "adsorbent", followed by ion exchange technique.

Moving to the third document cited by the Examiner viz. WO 01/52838, (hereinafter referred to as Zhang et al.) it should be noted that it has a first filing date of Jan 20, 2000, which is much later to that of Agharkar et al. and Anevski et al.

As per the claims of Zhang et al., the inventiveness of their application resides in a method of purification of Cremophor, which does not take recourse to chromatography/ adsorption as utilized by Agharkar et al. and Anevski et al.

The method of Zhang et al. comprises:

i) preparation of a suspension of Cremophor and activated charcoal;

ii) heating the suspension at a temperature of about 30°C to 60°C for a period of 1 h to 6 h; and

iii) filtering the heated suspension to separate the activated charcoal from Cremophor to give pure Cremophor, free of colorants and alkali metal cations. [Please refer to Lines 31-32, Page 1 and Lines 1-13, Page 2]

Even though, Zhang et al. claim that their method does not involve chromatography, however the statement " the treatment or purification process removes impurities from the castor oil. The main impurities removed include colorant

........and alkali metal cation such as K+, Na+ in Lines 1-4, Page 4 implies that once again an adsorption technique is utilized for purification. This is so because activated charcoal is a known "adsorbent", which adsorbs the colorant, impurities, ions etc. to provide Cremophor of desired purity.

From the foregoing, it would be abundantly evident that all the three document i.e. Agharkar et al:, Anevski et al., and Zhang et al. relate to a method for purification of Cremophor and use of such purified Cremophor for production of a stable paclitaxel formulation. Even though, the method utilized for purification of Cremophor might arguably be different, however, it need not be over emphasized that the basic underlying principle of such methods is removal of impurities, colorant, ions, etc through an "adsorption technique".

Against this background, the invention, embodied in the subject US Application No. 10/626,501, although, relating to a method of purification of Cremophor and utilization of the same for providing a stable paclitaxel composition, is different or is distinguished from the prior art, especially the three documents cited by the Examiner in that it does not take recourse to an "adsorption technique" for purification, but rather utilizes a "partition technique" for obtaining pure Cremophor.

In US Patent Application 10/626,501, in the first place, it should be noted that, amongst others, two of the documents cited by the Examiner viz. Agharkar et al. and Anevski et al., are discussed as prior art and stated that previous efforts to develop a shelf stable paclitaxel composition have certain limitations and hence were not successful. Agharkar, et al., is discussed in paragraph [0008] and Anevski, et al., is discussed in paragraph [0012].

The solution to the problem described and claimed in this application comprises a highly selective and novel method for purification of Cremophor involving "reverse phase chromatography", the process for purifying Cremophor comprising the steps of:

a) forming a solution of the Cremophor in alcohol and water, with or without the aid of heating;

b) loading this solution on to a chromatography column packed with reverse phase silica;

c) running the chromatograph using de-ionized water as the mobile phase to purify the Cremophor;

d) running the chromatograph using an eluent to recover the purified Cremophor; and

e) evaporating the residual water and the eluent. (See claim 1 and amended claim 21).

Reverse phase chromatography, which is also referred to, as "partition chromatography" is distinctly different from normal phase chromatography or adsorption chromatography in the following respects :

1. It should be noted that there are basically two principles of separation of a mixture of compounds via. Adsorption and Partitioning.

2. In the separation through Adsorption, commonly referred to as Normal Phase Chromatography the Mobile Phase is non-polar and the stationary Phase is polar. In such a method, which utilizes the polarity differences, the compound mixture to be separated is either mixed/slurried or loaded on to a column containing the adsorbent. The stationary Phase being polar retains or adsorbs the polar compounds, whereas the non-polar compounds are eluted into the Mobile Phase through use of a suitable eluent to effectively separate the polar and non-polar compounds.

   The adsorbents normally include aluminum oxide (both basic and neutral) and silica gel.

3. In the case of purification of Cremophor through adsorption over silica gel or aluminum silicate, the polar basic and acidic compounds are preferentially retained/adsorbed over Cremophor by the adsorbent used resulting in giving the Cremophor free or containing a reduced amount of such polar acidic and basic impurities.

4. In the separation through Partitioning, commonly referred to as Reverse Phase Chromatography the Mobile Phase is polar and the Stationary Phase is non-polar.

5. In such a method, which utilizes the solubility properties/difference of the compound mixture to be separated, the sample component in a suitable solvent/elution medium is passed through the Reverse Phase Chromatography column, whereby the partitioning mechanism starts operating continuously. Depending on the extractive power of the eluent, a greater or lesser part of the sample component would be retained reversibly by the Stationary Phase. The larger the fraction retained in the column, the slower the sample components will move down the column.

6. An example of the method claimed in US Application No. 10/626,501 the (impure) cremophor EL/ELP is mixed with a mixture of ethanol and water to provide a homogeneous solution of the Cremophor (the sample component) in a mixture of ethanol and water (the eluent). The solution is loaded on to Reverse Phase Column containing C8 and C18 silica gel and the column is eluted with ion free water, which acts as the Mobile Phase carrying forward the polar acidic and basic impurities. Once the impurities are effectively removed, the retained/adsorbed Cremophor is eluted using solvents/eluents selected from methanol, ethanol, isopropyl alcohol, or acetone, preferably acetone to give fractions of pure Cremophor, which can be isolated after removing the solvent by evaporation.

7. Silica gel, which is essentially silicic acid, $(H_2Si)_3$ or otherwise referred to as precipitated silica gel is in the form of lustrous granules, in which the Silicon (Si) atom is bonded to hydroxy group (-OH). The presence of such Si-OH bonds makes silica gel adaptable for use as an adsorbent National in Phase Chromatography for separation of various compound mixtures.

8. In Reverse Phase Chromatography or Partition Chromatography, the Silicon atom is bonded to oxygen (O) atom, in turn bonded to hydrocarbon (carbon) chains rather than to hydrogen (H) atoms as in the case of silica gel used in Adsorption Chromatography. These hydrocarbon chains represent the lipophilic phase (C2 to C18), while the aqueous mixture of the organic solvent surrounding the particle represents the hydrophilic phase. In Reverse Phase Chromatography, hydrophilic compounds will always move faster than hydrophobic ones, since the Mobile Phase is always hydrophilic than the Stationary Phase.

It is noted that PCT Application (PCT/US2003/023243) was filed on the same day as the present Application (US 10/626,501) viz. on Jul 24, 2003. The PCT Application was published as WO 2005/017079 on Feb 24, 2005.

The PCT Application was searched by the European Patent Office and in their search they had cited WO 01/52838, WO 00/23070, US 5,504,102 and WO 98/57630, of which one would note that Agharkar et al. (corresponding to US 5,554,102) Anevski et al., US 6,388,112 (corresponding to WO 0023070) and Zhang et al. (corresponding to WO 01/52838) were cited.

Subsequent to issuance of the Search Report, a Request for International Preliminary Examination was made and the International Preliminary Examination Report issued by the European patent Office on May 2, 2005 has found claims 16,17, 21-25 as not only novel but also involving an inventive step.

In the report, the Examining Authorities have commented with respect to the reverse chromatographic method claimed, "Given the importance of the polyethoxylated castor oil derivatives both in the pharmacokinetics and in the toxicology of taxol preparation, many prior art items deal with their purification. However, none of the cited prior art items uses nor hints to a reverse phase chromatographic process as disclosed in claim 1."

This clearly indicates that the method of purification claimed in the present US Application No. 10/626501, viz. process claims 1-14 and 18-20 could be construed to be novel and inventive and not anticipated from the teachings of Agharkar et al., Anevski et al. and Zhang et al.

For the Examiner's convenience, copies of the published PCT Application WO 2005/017079, as well as the International Preliminary Examination Report received from European Patent Office are attached.

Based on this and the explanation provided above it is clear that none of the cited references disclose all of the elements of the claims and thus, none of the references anticipate the claims.

In addition, there is no combination of the references which disclose or suggest the claimed invention. In particular, the process claims 1-15 and 18-20 are novel nonobvious and hence allowable. Claims 16-17 and 21-30 are also novel, nonobvious and patentable.

As discussed above, there are clear differences between Agharkar et al, Anevski et al, and Zhang et al., and the method described in this US Application No. 10/626,501.

With regard to rejection of composition claims 16-17 and 21-30, as mentioned hereinbefore, of the three documents cited by the Examiner, two of them viz. Anevski et al. and Zhang et al. have a filing date later than that of Agharkar et al. Incidentally, Zhang et al.'s Application has been abandoned. (See attached printout from the online public File Insepection)

Again as mentioned hereinbefore, the issued US 5,504,102 to Agharkar et al. contains a total of 20 claims of which claims 1-9 relates to a stabilized paclitaxel composition and claims 10-20 relates to method of preparing the said stabilized composition.

From the reading of specification and the claims of Agarkhar et al., it would be noted that the stabilized composition disclosed therein is directly related to the specific method for its manufacture, comprising treatment of commercially available Cremophor EL with an acid or alumina to give a purified Cremophor EL, which when utilized in the formulation provides stability to the composition. To say in other words, it could be considered as "product by process" claims.

The issued US 6,388,112 of Anevski et al. contains a total of 28 claims, of which claims 1-15 and 20-28 relate to a process for purification of Cremophor and claims 16-19 relate to a stabilized pharmaceutical composition of paclitaxel comprising the purified Cremophor obtained by the process claims 1-15 and 20-28.

In the present context relating this US Application No. 10/626,501,it is noted that the Examiner has rejected the composition claims 16-17 and 21-30 as unpatentable over Anevski et al., Agharkar et al., and Zhang et al., even though the method disclosed for purification of Cremophor is distinctly different from that reported in the abovementioned three documents. If this is so, it would seem that the composition claims of US 6,388,112 of Anevski et al. should also be held unpatentable over Agharkar et al., since it would have been held anticipated from Agharkar et al. The very fact that both the composition and process claims of Anevski et al. have been considered for allowance over the teachings of Agharkar et al., clearly indicates that not only the method for purification of Cremophor and its use for preparing a stabilized pharmaceutical composition of Paclitaxel as taught by Anevski et al. is considered to involve an inventive step and hence patentable over Agharkar

et al. It is noted that Agharkar is cited as prior art on the cover page of US Patent 6,388,112.

US Patent 6,710,195 (Assigned to SuperGen, Inc.; First filed on Nov 26, 2001; Issued on March 23, 2004). This patent describes a method for treatment of Cremophor by heating under various conditions and parameters, recited therein to give a Cremophor having pH in the range of 4-4.5, which when utilized in a paclitaxel formulation is found to render stability to such a formulation. US Patent 6,710,195 contains claims both for process (purification of Cremophor) as well as for compositions.

US Patent 6,071,952 (Assigned to Mylan Pharmaceuticals, Inc.; First filing date of Dec 02, 1998; Issued on 6, June 06, 2000) and US Patent 6,153,644 (Assigned to Mylan Pharmaceuticals, Inc.; First filing date of Dec 02, 1999; Issued on Nov 28, 2000), collectively refer to a stabilized paclitaxel formulation wherein the stabilization is achieved through addition of an antioxidant especially sodium metabisulfite.

US Patent 6,306,894 (Assigned to NaPro Biotherapeutics, Inc.; First filing date of Dec 22, 1992; Issued on date: Oct 23, 2001). This patent describes a pharmaceutical composition of paclitaxel and polyethoxylated castor oil, acidified by mixing with an acid, especially citric acid.

Even though, the patents of Mylan and Napro explicitly do not refer to a method for purification of Cremophor but rather to a method of stabilization of a paclitaxel composition through addition of an antioxidant and acid, however, these patents need to be taken into consideration for the arguments, which will follow later.

From SuperGen's, US Patent 6,710,195, it is apparent that the only difference it has from Agharkar et al. and Anevski et al. is in the method for purification/ treatment of Cremophor and only the process per se should have been allowed . However, the fact that composition claims comprising purified/ treated Cremophor have been allowed is a testimony that in all probability it is found to give "a product by a distinctly different process" and hence, not anticipated over such prior art methods/compositions, especially Agharkar et al. and Anevski et al.

The above fact reinforces that since a distinctly different method for purification of Cremophor is described and claimed and utilized for providing a stable composition of paclitaxel, both the process and composition claims ought to be allowed because the product by being prepared with the purified non-ionic solvent is novel and nonobvious.

Again turning back to all the documents referred hereinbefore, it should be noted that:

i) The inventive step residing in Agharkar et al. lies in treatment of Cremophor with an acid or alumina, wherein such a treatment results in providing a

material with reduced carboxylate anion content, which in turn helps in stabilization of paclitaxel composition.

However, if one refers to Table 4, Column 9 of Agharkar et al., wherein a taxol composition containing an acid such as HCl or HNO_3 when stored for 56 days at 50°C shows a drop in pH from the initial value, indicating that "some acid is generated in situ during storage" which might be the factor behind stabilization of composition.

ii) In the case of Anveski et al. (purification of Cremophor with activated carbon), it might be noted that, in general, activated carbon is acidic in nature and in principle it could be considered treatment of Cremophor with an acid, which may be the factor helping in stabilization of the composition.

iii) In the case of Zhang et al., wherein the method comprises mixing and heating of castor oil and activated charcoal under 30°C to 60°C for a period 1 to 6 h based on the description on Page 6, Lines 20-22, it would be apparent that the untreated Cremophor is reported to have pH of 6.06, whereas the Cremophor treated by such a method is found to have pH of 4.27, which again indicates that there is a drop in pH on purification, in turn implying that an acid is generated in situ.

Further, they then use an acid in the composition for stabilization and effectively it could be the combination of treatment method and addition of acid, which stabilize the formulation.

iv) In US Patent 6,071,952 of Mylan Pharmaceuticals, Inc. a stabilized paclitaxel formulation is achieved through addition of sodium metabisulfite.

It should be noted that sodium metabisulfite dissociates in water to give sodium bisulfite ($NaHSO_3$) or sodium salt of sulphurous acid (HSO_3). It could be argued that obviously sulphurous acid is the agent, which helps in stabilization of the solution, once again a case of stabilization through an acid.

v) In the case of US Patent 6,306,894 of NaPro Biotherapeutics, Inc., paclitaxel and polyethoxylated castor oil is acidified by mixing with and acid, especially Citric acid to obtain a stabilized pharmaceutical composition.

From all the above, it might be noted that stabilization of a paclitaxel composition has been achieved either through utilization of Cremophor having an acidic pH, adding extraneous acid or antioxidant, which not only reduces the pH further but also generates an acid *in situ* on storage.

Contrary to the above, in the method for purification of Cremophor as well as formulation of a paclitaxel composition as taught in this US Application No. 10/626,501, neither an acid is added nor any acid is generated *in situ*. To say in other words, the stability exhibited by the pharmaceutical composition of paclitaxel as obtained by the method of this US Application No. 10/626,501 does not take

recourse to addition of an extraneous acid or generation of acid *in situ*, for achieving the stability, which renders it distinctly different from the prior art compositions.

A testimony to the above fact could be seen from comparative stability profile of the paclitaxel composition prepared by the process embodied in the US Application No. 10/626,501 vis-à-vis that of paclitaxel compositions available in the market. In particular Dabur has carried out a comparative study of the cited composition with respect to the following marketed compositions viz.

a) "Taxol" of the innovator, Bristol Myers- Squibb; and

b) "Paclitaxel", of IVAX, a generic manufacturer.

The "Taxol" composition of Bristol Myers - Squibb is in all probability manufactured as per the method described in US 5,504,102 of Agharkar et al., wherein the Cremophor is either treated with an acid, especially HCl or with a bed of Alumina prior to formulating the composition.

With regard to the "Paclitaxel" formulation of IVAX, it could be seen from its approved Label Insert that IVAX's paclitaxel solution contains paclitaxel, polyoxyl 35 castor oil, citric acid and alcohol, which is essentially the teaching of US 6,306,894 of NaPro Biotherapeutics, Inc. Attached is a copy of the approved Draft Label of the "Paclitaxel" formulation of IVAX.

All the abovementioned three samples were kept on stability for six months at 40± 2° C, 75±5% RH (Upright). At the end of six months of storage, not only the assay but also the pH of the solution were measured and compared with the initial values. The results obtained are summarized in Table 1.

Table-I : Comparative pH And stability Profile Of Paclitaxel Compositions Prepared As the Method of Our US Application No. 10/626,502; Marketed "Taxol" Composition Of Bristol Myers-Squibb; And The Marketed "Paclitaxel" Composition Of IVAX

Parameters	Bristol Myers-Squibb's Marketed "Taxol" Composition		IVAX's Marketed "Paclitaxel" Composition		Composition Prepared As Per The Method Of The Present US Application No. 10/626,501	
	Initial	After 6 months @ 40± 2° C/ 75±5% RH (Upright)	Initial	After 6 months @ 40± 2° C/ 75±5% RH (Upright)	Initial	After 6 months @ 40± 2° C/ 75±5% RH (Upright)
pH: 9 to 10 (solution	4.65	5.01	4.35	5.08	4.80	4.91

in water for injection)						
Assay of Paclitaxel (mg/ml)	6.15	6.02	6.13	6.03	6.14	6.08

From Table 1, it can be seen that in case of Bristol Myers- Squibb formulation, there is a rise in pH from 4.65 to 5.01 on storage and drop in assay on storage of about 2.11 %; in the case of the IVAX formulation, there is rise in pH from 4.35 to 5.08 and drop in assay of about 1.63%; whereas in case of the formulation prepared as per the method disclosed in this US Application No 10/626,501, there is no significant change in pH of the solution on storage whereas the drop in assay on storage is only just about 0.98%.

The above comparison clearly indicates that the composition prepared as per method disclosed in this US Application No 10/626,501 exhibits:

i) better stability as compared to Bristol Myers-Squibb's and IVAX's formulations; and

ii) no appreciable change in pH.

The later point i.e. that the claimed composition exhibits no appreciable change in pH again reinforces that no acid is generated in situ in the claimed composition, which coupled with the better stability of the composition, is indeed novel and inventive, and in no way can claims 16-17 and 21-30 of this US Application No 10/626,501 be construed to be anticipated or obvious from the teachings of Agarkhar et al., Avenski et. al., and Zhang et al.

Accordingly, it is submitted that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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